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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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02/27/1997

VICTOR SMIT

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FITCH, EVEN, TABIN & FLANNERY
P. O. BOX 18415
WASHINGTON, DC 20036

EXAMINER

BOESEN, AGNIESZKA

ART UNIT

PAPER NUMBER

1648

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 08/807,506	Applicant(s) SMIT ET AL.	
	Examiner AGNIESZKA BOESEN	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 94-111, 133 and 136-141 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 94-111, 133 and 136-141 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 9, 2009 has been entered.

Claims 94 and 110 have been amended. Claims 94-111, 133, and 136-141 are pending and under examination.

Claim Rejections - 35 USC § 102/ *Claim Rejections - 35 USC § 103*

Rejection of claims 94-103, 106, 107, 109, 110, 111, 137-141 under 35 U.S.C. 102(b) as being anticipated or in the alternative under 35 U.S.C. 103(a) as being obvious over Smit et al. (Biochemical and Biophysical research communications, 1992, Vol. 187. in IDS of November 14, 2007) **is withdrawn** in view of Applicant's amendment and arguments.

Rejection of claims 94-100, 104-109, 133, 136, 137, 138, 140 and 141 under 35 U.S.C. 103(a) as being unpatentable over Smit et al. (Electrophoresis, 1994, Vol. 15, p. 251-254) in view of Smit et al. (Biochemical and Biophysical research communications, 1992, Vol. 187. in IDS of November 14, 2007) and Builder et al (US Patent 4,511,502) **is maintained** and it is reformulated below to include the newly amended limitations.

New Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 94-111, 133 and 138-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smit I et al. (Biochemical and Biophysical research communications, 1992, Vol. 187, in IDS of November 14, 2007) in view of Smit II et al. (Electrophoresis, 1994, Vol. 15, p. 251-254).

Smit I teaches a method of structure function analysis using mass spectrometry to monitor chemical modifications of zinc binding domain of IL-3, comprising gradual chemical modification of IL-3, monitoring the modification reaction, protease treatment, mass spectrometry, and assaying biological activity of the modified product (see the entire document). Smit teaches chemical modification of IL-3 amino acid residues His²⁶, Lys²⁸, His⁹⁵, His⁹⁸, and Lys¹⁰ wherein protein digestion is performed using endoproteases Endo Glu and Endo Lys C and exoproteases carboxypeptidase Y (see page 859, Materials and Methods, and Figure 1). Smit I teaches that chemical modifications of IL-3 result in loss of IL-3 binding zinc. It is noted that zinc taught in Smit inherently comprises the catalytic binding center and the peptides inherently comprise the receptor binding center. With regard to claim 139, it is noted that it is expected that the modified IL-3 disclosed by Smit I would have the properties to inhibit native IL-3 as require by the claims, absent any evidence on the contrary.

Smit I does not expressly teach the method step of applying chemical modifications of IL-3 to specifically directed to the catalytic center of the protein resulting in enhanced stability,

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suppressed antigenicity, acquired antagonistic activity, or cell inhibitory activity without distortion of receptor binding activity.

Smit II teaches mild and sensitive electrophoresis method and circular dichroism spectroscopy (which is a type of mass spectroscopy) to monitor chemical modifications of human interleukin-3 (see the entire document). Smit teaches gradual chemical modification of IL-3 by alkylation with acetic anhydride and proteases under pH of between 5.7 and 7.0 and in the presence of phosphate buffer (see pages 251 and 252). Smit teaches that chemical modifications of IL-3 result in conformational changes of IL-3 resulting in shift in electrophoretic mobility (see page 253).

Smit II does not expressly disclose step e) of the present method: “assaying biological activity of the modified product”.

However it would have been obvious that the loss of IL-3 capability to bind zinc would result in an antagonistic activity without distortion of receptor binding activity of IL-3 because Smit I discloses that zinc binding activity of IL-3 is involved in phosphorylation of IL-3 receptor. Thus an unmodified IL-3 ligand that is an agonist (receptor stimulator) when modified would be expected to become an IL-3 receptor antagonist (blocking receptor function and cascade of cellular events following receptor activation) as a results of the loss of its agonist activity due to inability to bind zinc. Thus the skilled artisan would have expected that loss of zinc binding activity of IL-3 will result in acquired antagonistic activity without distortion of receptor binding activity as presently claimed.

It would have been obvious that Smit's chemical modifications of IL-3 would result in a change of IL-3 function, wherein the change is an acquired antagonistic or inhibitory activity of

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IL-3, because Smit I (1992) disclose that chemical modification of IL-3 results in inability of IL-3 to bind zinc and that zinc binding activity of IL-3 is involved in phosphorylation of IL-3 receptor. Thus an unmodified IL-3 ligand, an agonist (receptor stimulator) when modified would be expected to become an IL-3 receptor antagonist (blocking receptor function and cascade of cellular events following receptor activation) as a results of the loss of its agonist activity due to inability to bind zinc.

The skilled artisan would immediately envisage assaying biological activity of the chemically modified IL-3 because the purpose of IL-3 modification is to alter its biological activity as evidenced by Smit I (1992). Thus it would have been obvious to assay the biological activity of chemically modified IL-3 because Smit I (1992) teaches that chemical modifications of IL-3 result in loss of IL-3 to bins zinc which affect IL-3 function.

Therefore the claimed invention would have been *prima facie* obvious to the skilled artisan at the time the invention was made.

Claims 136 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smit I et al. (Biochemical and Biophysical research communications, 1992, Vol. 187. in IDS of November 14, 2007) in view of Smit II et al. (Electrophoresis, 1994, Vol. 15, p. 251-254) as applied to 94 and 108 and further in view of and Builder et al (US Patent 4,511,502).

Smit I and Smit II teach the limitations of claims 94-111, 133 and 137-141 as discussed above. Neither Smit I or Smit II teach using urea or EDTA.

It would have been *prima facie* obvious to use urea and EDTA in the method of Smit (1994) because as evidenced by Builder, urea and EDTA are commonly used chelating agents to prevent protease degradation and precipitation of the protein. EDTA is commonly used as a

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chelating agent and urea is added to maintain protein solubility. In the present case, the skilled artisan would have been motivated to maintain the stability of the IL-3 protein while performing chemical modifications. The skilled artisan would have been motivated to prevent IL-3 from precipitating from the solution by adding urea.

Thus the present invention would have been *prima facie* obvious to the person skilled in the art at the time when the invention was made.

Response to Applicant's arguments

It is noted that in the Remarks of February 9, 2009 Applicant refers to a Declaration by Dr. Smit. However Applicant failed to submit the said Declaration. Examiner will consider the Declaration by Inventor Dr. Smit once the Declaration is submitted by the Applicant.

Applicant's arguments have been fully considered but fail to persuade. Applicant argues that there is no evidence based on the art of record that describes or suggests that protein and peptides have two distinct centers –the receptor binding center and the catalytic activity center. Applicant argues that there is no evidence in the art of record that suggests quantitative structure function analysis that involves position specific modification of the catalytic center without distorting the receptor binding center.

In response the Examiner notes that the receptor binding center and the catalytic activity center are inherently present in the IL-3 protein and in the Zinc respectively, taught by Smit I and II, as discussed in the rejection above. With regard to the quantitative structure function analysis that involves position specific modification of the catalytic center without distorting the receptor binding center, the Examiner notes that since the present method claims would have been obvious over the combination of Smit I and Smit II, the skilled artisan would have expected that

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the method steps taught by Smit I and II would have resulted in modification of the catalytic center without distorting the receptor binding center as presently claimed.

Thus the claims would have been obvious to the skilled artisan at the time of the present invention and in the absence of the evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 94-111, 133 and 136-141 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 54-68 of copending Application No. 11/979,278. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of this and the copending application are drawn to methods comprising quantitative structure function analysis and applying specific chemical modifications of amino acids within the proteins and comprising

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monitoring the modification reaction, protease treatment, mass spectrometry and assaying biological activity of the modified product.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AGNIESZKA BOESEN whose telephone number is (571)272-8035. The examiner can normally be reached on 9:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen/

Examiner, Art Unit 1648